REMARKS

Claims 1-104 are currently pending. Claims 3-98 are withdrawn pursuant to a restriction requirement. Claim 102 has been amended. The amendment to claim 102 does not constitute new matter.

The Examiner has rejected claim 102 under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. The Examiner has rejected claims 1-2 and 99-103 under 35 U.S.C. § 103(a) as being allegedly obvious over MacPhee *et al.* (U.S. Patent No. 6,054,122) ("MacPhee") in view of Burnouf (Colloque INSERM, 1989, 175:373-381) ("Burnouf") and Racanelli *et al.* (U.S. Patent No. 5,254,536) ("Racanelli"). The Examiner has rejected claims 1-2 and 99-104 under 35 U.S.C. § 103(a) as being allegedly obvious over MacPhee in view of Burnouf and Racanelli, and in further view of Stroetmann (U.S. Patent No. 4,442,655) ("Stroetmann"). The Examiner has rejected claims 1-2 and 99-104 under 35 U.S.C. § 103(a) as being allegedly obvious over Stroetmann in view of MacPhee, Burnouf, and Racanelli. For reasons detailed below, the rejections should be withdrawn and claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

Claim 102 is Definite

The Examiner has rejected claim 102 under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. The Examiner states that "it is unclear if a carrier material is subjected to viral decontamination and then combined with the active agents or if 'one or more of the active agents' are applied to the carrier material and the resulting composition comprising the active agents and the carrier are subjected to viral decontamination." Applicants note that claim 102 has been amended to recite:

> 102. (Currently amended) The medicament of claim 1, wherein one or more of the active agents, which have been subjected to a process selected from the group of virus depletion, virus inactivation, and a combination thereof, are applied on carrier materials, which have been subjected to a process selected from the group of virus depletion, virus inactivation, and a combination thereof.

Applicants assert that claim 102 now more particularly recites that the active agents and the carrier materials are each virally decontaminated prior to combining. Accordingly, Applicants assert that the Examiner's rejection has been obviated, and respectfully request that the rejection be withdrawn.

Claims 1-2 and 99-103 Are Not Obvious Over MacPhee, Burnouf, and Racanelli

The Examiner has rejected claims 1-2 and 99-103 under 35 U.S.C. § 103(a) as being obvious over MacPhee *et al.* (U.S. Patent No. 6,054,122) ("MacPhee") in view of Burnouf (Colloque INSERM, 1989, 175:373-381) ("Burnouf") and Racanelli *et al.* (U.S. Patent No. 5,254,536) ("Racanelli"). The Examiner states that MacPhee discloses "fibrin sealant compositions comprising purified, lyophilized fibrinogen, plasminogen, Factor XIII (transglutaminase) that are of human origin and which are virally inactivated," and asserts that the human origin of the active agents meets the limitation of allogenic sources. The Examiner further states that MacPhee discloses the use of a dehydrating agent and that fibrin sealant components are "traditionally disposed in separate containers." The Examiner acknowledges that MacPhee does not teach the use of a serpin protease inhibitor ("serpin") that does not inhibit elastase or collagenase, or that the serpin is separately sterilized. However, the Examiner asserts that Racanelli teaches the use of a serpin, and that Burnouf teaches separate sterilization. The Examiner further asserts that it would have been obvious to a person of ordinary skill in the art to combine the references to reach the present invention.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See MPEP §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

There is no suggestion or motivation to combine MacPhee with Burnouf and Racanelli, because none of the references teach the addition of serpins or the separate viral inactivation of serpins. Burnouf and Racanelli do not provide the requisite suggestion or motivation to add serpins to the composition of MacPhee. Burnouf makes no reference to serpins at all. While Racanelli identifies the use of serpins, Racenelli states that "no synergistic effect for combined thrombin... and rPAI-1... was observed," and in fact discloses data showing that the combination of thrombin and PAI-1 is no better than thrombin or PAI-1 administered individually. See Racanelli at col. 8, lines 30-48, in particular at Table 1. Thus, a person of ordinary skill in the art would not be motivated to add serpins to the composition of MacPhee, which contains thrombin, because Racanelli shows that no additional benefit would arise by adding serpins to a composition that already contained thrombin. Furthermore, even if one assumes that serpins are present, neither Racanelli nor Burnouf teaches or suggests viral inactivation of serpins separate from other active agents. Racanelli makes no reference to the separate viral inactivation of

serpins. Burnouf makes no reference to serpins, and does not specifically state that serpins must be virally inactivated separately from other active agents. Burnouf merely states that different viral inactivation techniques are required for different compounds; Burnouf does *not* say that they must be treated separately, only that different techniques are needed. See Burnouf at page 373 ("Various virus inactivation treatments... are applied during the purification process while others can, in some instance, be performed on the final product."). Burnouf teaches that some active agents may be virally inactivated as "a final product" with other active agents present. *Id.* Thus, a person of ordinary skill in the art would not be motivated to single out serpins to be treated separately from other active agents based upon the teachings of Burnouf, because they would not know whether serpins must be virally inactivated during purification or may be virally inactivated as a final product. Lastly, MacPhee discloses a foam, whereas the present invention discloses a liquid or solid tissue sealant. See MacPhee at col. 32, line 1 to col. 33, line 55; see specification at page 5, and original claim 100. A person of ordinary skill in the art would not be motivated to combine the cited references to produce a solid or liquid, since the disclosed form of the composition of MacPhee is a foam. Accordingly, a person of ordinary skill in the art would not be motivated to add a serpin to the composition of MacPhee, and to virally inactivate the serpin separately from any other active agents.

The references cited by the Examiner do not teach all of the limitations of the present invention. As noted above, Racanelli and Burnouf do not specifically state that the serpins must be virally inactivated outside of the presence of the other active agents, but merely states that different active agents must be virally inactivated in different manners. As such, MacPhee, Burnouf, and Racanelli do not teach the limitation that if the serpin is virally inactivated, the treatment "is not applied in the presence of one or more of the other active agents."

Furthermore, although MacPhee does refer to $CaCl_2$ as a drying agent, it does not disclose the use of $CaCl_2$ to solidify the allogenic provisional matrix; in fact, the $CaCl_2$ is added to the already dry composition "to accelerate the speed of fibrin formation." See MacPhee at col. 28, lines 51-59. Accordingly, the references cited by the Examiner do not teach separate viral inactivation of serpins or the use of dehydrating agents to solidify the allogenic provisional matrix, and therefore do not teach all of the limitations of the present invention.

Based upon the foregoing arguments, Applicants submit that the Examiner has not established a *prima facie* case of obviousness, and respectfully request that the rejection be withdrawn.

Claims 1-2 and 99-104 Are Not Obvious Over MacPhee, in view of Burnouf, Racanelli, and in further view of Stroetmann

The Examiner has rejected claims 1-2 and 99-104 under 35 U.S.C. § 103(a) as being allegedly obvious over MacPhee in view of Burnouf and Racanelli, and in further view of Stroetmann (U.S. Patent No. 4,442,655) ("Stroetmann"). The Examiner acknowledges that MacPhee does not teach the solidification of fibrin by use of a dehydrating agent and an allogenic transglutaminase. However, the Examiner asserts that it would have been obvious to modify the composition of MacPhee with the teachings of Burnouf and Racanelli, as stated above, and to further modify the composition by adding a dehydrating agent and transglutaminase as taught by Stroetmann.

Applicants submit that, as set forth above, a person of ordinary skill in the art would not have the suggestion or motivation to combine MacPhee, Burnouf, and Racanelli to reach the present invention, and that these three references do not contain all of the limitations of the

present invention. Applicants further submit that Stroetmann fails to provide the missing motivation or limitations.

Applicants assert that Stroetmann does not provide any suggestion or motivation to virally inactivate serpins separately from other active agents. As noted above, neither MacPhee, Burnouf, or Racanelli provides a suggestion or motivation to virally inactivate serpins separately from other active agents. Stroetmann fails to provide a suggestion or motivation to perform this step, and in fact states that the final product is sterilized after packaging, *i.e.*, with all active agents present. See Stroetmann at col. 11, lines 5-10. Stroetmann also merely refers to sterilization, not viral inactivation. *Id.* Thus, a person of ordinary skill in the art would not be motivated to separately virally inactivate the active agents based upon Stroetmann. Furthermore, Applicants assert that a person of ordinary skill in the art would not be motivated to modify MacPhee by adding a dehydrating agent to solidify the provisional matrix. Contrary to the Examiner's assertion, Stroetmann does not disclose dehydrating agents to solidify the provisional matrix, but instead discloses the use of organic solvents to increase the solubility of the active agents in solution. See Stroetmann, col. 3, lines 45-58. The dry preparation of Stroetmann is dried via freeze-drying, not via dehydrating agents. See Stroetmann, col. 3, lines 11-36. In contrast, the present invention utilizes dehydrating agents to remove water and solidify the provisional extracellular matrix. See specification at page 7 and 10. Based upon the teaching of Stroetmann, a person of ordinary skill in the art would not be motivated to add an organic solvent to the composition of MacPhee such that "the allogenic provisional matrix is solidified by the use of dehydrating agents." Based upon the teaching of Stroetmann, a person of ordinary skill in the art would in fact solidify the composition of MacPhee by freeze-drying, because Stroetmann states that freeze-drying provides "surprisingly high stability." See Stroetmann at col. 3, lines 9-

16. Accordingly, a person of ordinary skill in the art would not be motivated to modify MacPhee by adding serpins that are virally inactivated separately from other active agents, or by using dehydrating agents to solidify the composition.

Applicants assert that the references cited by the Examiner do not teach all of the limitations of the present invention. As discussed above, MacPhee, Burnouf, and Racanelli do not specifically teach serpins or viral inactivation of serpins separate from other active agents, nor do they teach the use of dehydrating agents to solidify the provisional matrix. Stroetmann fails to teach the addition of a serpin protease inhibitor which is virally inactivated separately from other active agents, and states that the final product is sterilized after packaging, *i.e.*, with all active agents present. See Stroetmann at col. 11, lines 5-10. As noted above, although Stroetmann discloses the use of organic solvents, they are used to increase solubility of active agents, and not to solidify the composition. Accordingly, Stroetmann, MacPhee, Burnouf, and Racanelli do not teach all of the limitations of the present invention.

Based upon the foregoing arguments, Applicants submit that the present invention is not obvious in view of the cited references, and respectfully request that the rejection be withdrawn.

Claims 1-2 and 99-104 Are Not Obvious Over Stroetmann in view of MacPhee, Burnouf, and Racanelli

The Examiner has also rejected claims 1-2 and 99-104 under 35 U.S.C. § 103(a) as being allegedly obvious over Stroetmann in view of MacPhee, Burnouf, and Racanelli. The Examiner states that:

> "It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the dry preparation taught by Stroetmann et al. by using the active agents from an allogenic source and adding a serpin that does not inhibit elastase or collagenase, wherein said serpin is sterilized separately from the other agents."

The Examiner further asserts that a person of ordinary skill in the art would be motivated to sterilize PAI-1 separately from the other active agents, and to use allogenic sources, based upon the teachings of Burnouf and MacPhee.

Applicants submit that the above arguments directed to the rejection over MacPhee in view of Burnouf and Racanelli, in further view of Stroetmann, apply equally to the rejection over Stroetmann in view of MacPhee, Burnouf, and Racanelli. Accordingly, Applicants assert that the cited references do not provide any suggestion or motivation to virally inactivate serpins separately from other active agents, and do not teach all of the limitations of the present invention.

Based upon the foregoing remarks, Applicants submit that the present invention is not obvious in view of the cited references, and respectfully request that the rejection be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the inventions described and defined by claims 1-2 and 99-104 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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